Petitioner Presentation to Neurological Devices Panel For Reclassification of Alpha-Stim® CES Devices From Class III to Class II

February 10, 2012

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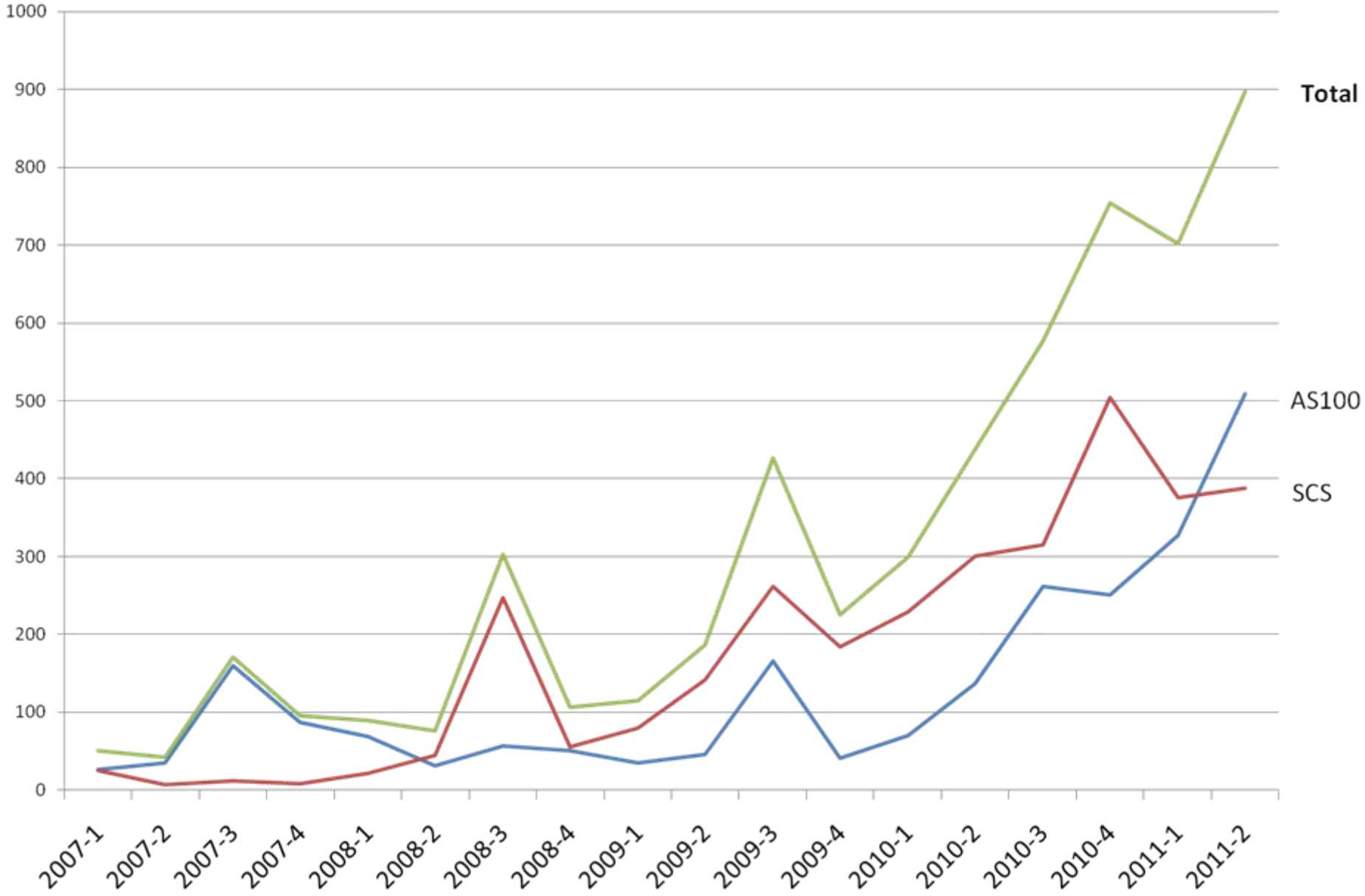
What is Alpha-Stim®?

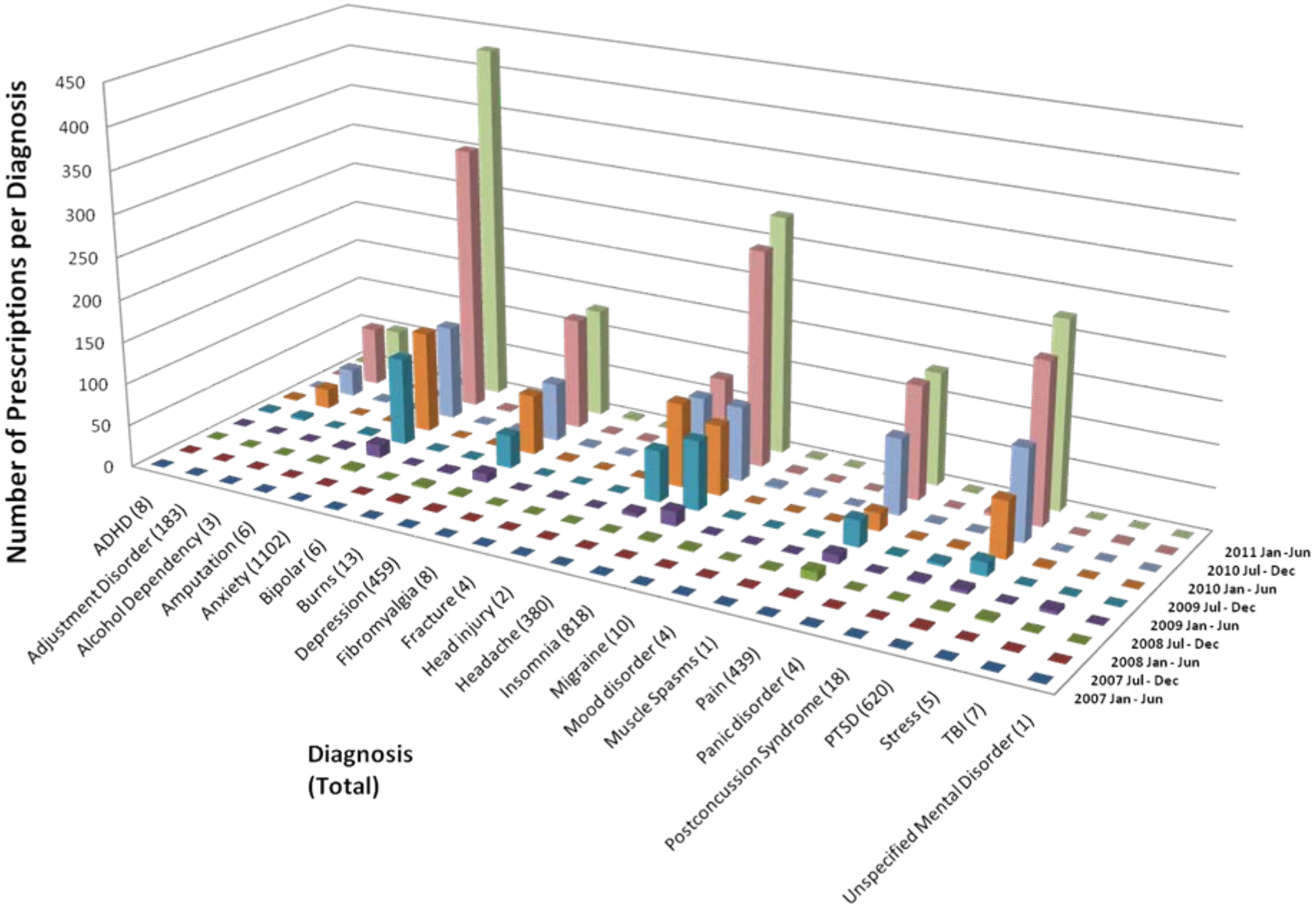
- Cranial electrotherapy stimulation (CES) device.
- On the market in the USA since 1981.
- FDA Cleared through the 510(k) process for the treatment of anxiety, insomnia and depression.
- In the USA sales of Alpha-Stim® are restricted by or on the order of a licensed health care practitioner.
- An estimated 8,248,920 Alpha-Stim® treatments were administered in the 5 year period between 2007 and 2011.
- ***Currently the biggest customer for Alpha-Stim® devices are the US Government (DOD and VA), State Governments (prisons, secured hospitals and substance abuse programs) followed by exports to China and Europe.***

Total US Government Alpha-Stim® Orders (DOD, VA and Tricare) Per Quarter

January 2007 - June 2011



All Diagnoses on Tricare Prescriptions For Alpha-Stim®
January 2007 - June 2011



All Diagnoses on Tricare Prescriptions for Alpha-Stim® (same data as prior graphic slide)

January 2007 - June 2011

	Jan-Jun 2007	Jul-Dec 2007	Jan-Jun 2008	Jul-Dec 2008	Jan-Jun 2009	Jul-Dec 2009	Jan-Jun 2010	Jul-Dec 2010	Jan-Jun 2011	Total
ADHD	0	0	0	0	2	2	0	1	3	8
Adjustment Disorder	0	0	0	0	4	24	33	70	52	183
Alcohol Dependency	0	0	0	0	0	0	2	0	1	3
Amputation	0	0	1	2	2	1	0	0	0	6
Anxiety	**0**	**0**	**3**	**16**	**105**	**121**	**113**	**317**	**427**	**1102**
Bipolar	0	0	0	0	1	0	1	2	2	6
Burns	0	2	3	2	1	0	2	1	2	13
Depression	**0**	**1**	**2**	**11**	**40**	**72**	**70**	**133**	**130**	**459**
Fibromyalgia	0	0	0	0	0	2	2	1	3	8
Fracture	0	0	0	1	0	0	1	2	0	4
Head injury	0	0	0	0	0	0	1	0	1	2
Headache	0	0	0	5	61	100	90	97	27	380
Insomnia	**0**	**0**	**2**	**18**	**83**	**84**	**89**	**258**	**284**	**818**
Migraine	0	0	2	0	1	0	3	2	2	10
Mood Disorder	0	0	0	0	0	0	2	1	1	4
Muscle Spasms	0	0	1	0	0	0	0	0	0	1
Pain	0	1	11	11	32	22	91	136	135	439
Panic Disorder	0	0	0	0	1	1	1	0	1	4
Postconcussion Syndrome	0	0	0	3	4	2	1	5	3	18
PTSD	**0**	**2**	**2**	**5**	**17**	**68**	**110**	**192**	**224**	**620**
Stress	0	0	3	0	0	2	0	0	0	5
TBI	0	0	0	5	0	0	0	2	0	7
Unspecified Mental Disorder	0	0	0	0	0	0	0	1	0	1

Pain Management Task Force

Final Report
May 2010

Office of The Surgeon General, US Army

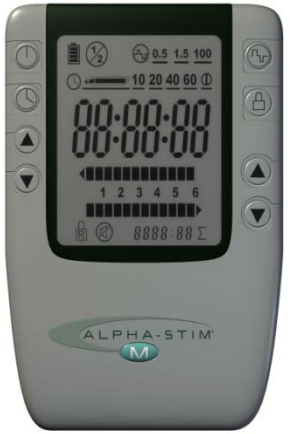
Providing a Standardized DoD and VHA Vision and Approach to Pain Management to Optimize the Care for Warriors and their Families

Figure 12: Tier II Modalities

Modality	Passive	Active
Movement therapy (Qi Gong, Tai Chi, Marital Arts)	Facility based classes	Self directed with video, exercising
Art Therapy	Facility based classes	Self expression through journaling, art, dance, etc.
Music Therapy	Facility based classes	Self directed with iPods, etc.
Aroma Therapy	Facility based treatment	Self directed
Cold Laser	Facility based treatments	N/A
Monochromatic Near Infrared Energy (MIRE) Treatments	Clinic based treatments	Self directed with MIRE personal equipment
Cranial Electrical Stimulation	Clinic based treatments	Self directed with CES personal equipment

How Does One Use Alpha-Stim® CES?

Segment from 30 minute patient training video



FDA History with CES and Alpha-Stim®

- CES has been on the market in the United States since the 1960s.
- CES was a "Pre-Amendment" device that was placed in Class III in 1976 until FDA could determine its proper classification, or require Pre-Market Approval (PMA).
- All legally cleared CES devices on the market since 1976 have been cleared under the 510(k) process of substantial equivalency.
- ***CES does not fit the Class III device classification in that sufficient evidence exists to determine if general or special controls provide reasonable assurance of safety and effectiveness and CES is not "life-supporting" or "life-sustaining."***
- ***Since 1981, EPI has filed five 510(k) applications, one PMA, and two petitions for reclassification with FDA, all which highlighted the proven safety and efficacy of the Alpha-Stim® CES device.***
- FDA proposed a rule in August 2011 requiring all CES device to submit a PMA. EPI then filed this Petition for Reclassification under consideration today.

Petition for Reclassification

Class II Devices are devices that are or eventually will be subject to special controls. A device is in class II if general controls alone are insufficient to provide reasonable assurance of its safety and effectiveness and there is sufficient information to establish special controls, *including the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidance documents, recommendations, and other appropriate actions* as the Commissioner deems necessary to provide such assurance.

21 C.F.R. §860.3(c)(2).

Safety and Effectiveness - 21 C.F.R. §860.7(b)

In determining the safety and effectiveness of a device for purposes of classification, establishment of performance standards for class II devices, and premarket approval of class III devices, the Commissioner and the classification panels will consider the following, among other relevant factors:

(1) The persons for whose use the device is represented or intended – ***anxiety, insomnia and depression are ubiquitous across all patient populations.***

(2) The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use – ***EPI agrees with and confirms the three indications of anxiety, insomnia and depression that our Alpha-Stim® CES device has been used for over the past 31 years.***

(3) The probable benefit to health from the use of the device weighed against any probable injury or illness from such use – ***EPI will establish here today the safety of Alpha-Stim® technology and proof of effectiveness in a number of studies revealing consistent results.***

(4) The reliability of the device –***EPI has 31 years of research, FDA inspections and safety data to confirm the device's reliability.***

Valid Scientific Evidence

Although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective. 21 C.F.R. §860.7(c)(1)(*emphasis added)*.

Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is ***reasonable assurance of the safety and effectiveness*** of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. 21 C.F.R. §860.7(c)(2)(*emphasis added*).

Given our time limitation today EPI is concentrating on Alpha-Stim® double-blind RCT studies but it has also provided FDA numerous additional research studies upon request in 2009 and 2011. Copies of those submissions have also been provided to this Neurological Devices Panel. When taken as a whole the studies previously provided and discussed herein support consistent findings of safety and effectiveness.

Reasonable Assurance of Safety

There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use. 21 C.F.R. §860.7(d)(1).

Unique to this type of forum, EPI comes to you today with 31 years of Alpha-Stim® CES data establishing it as an extremely safe technology.

Reasonable Assurance of Effectiveness

There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results. 21 C.F.R. §860.7(e)(1). The valid scientific evidence used to determine the effectiveness of a device shall consist principally of well-controlled investigations, unless the Commissioner authorizes reliance upon other valid scientific evidence which the Commissioner has determined is sufficient evidence from which to determine the effectiveness of a device, even in the absence of well-controlled investigations. 21 C.F.R. §860.7(e)(1).

EPI has an abundance of well controlled investigations amassed over 31 years of encouraging research by independent government and university investigators in the form of mechanistic studies using fMRI, LORETA, EEG, EMG and other diagnostic tests as well as double-blind randomly controlled trials and less rigid research models. This is further supported by post marketing surveillance in the form of several comprehensive scientifically valid user surveys.

Special Controls

EPI has self imposed special controls for nearly two decades that compare closely with those of rTMS that were recently adopted by FDA in establishing rTMS as a Class II device.

Self Imposed Special Controls **Implemented for Alpha-Stim® CES by EPI** **In Practice by EPI Since 1990s**	**Class II Special Controls for** **Repetitive Transcranial Magnetic Stimulation (rTMS)** **Finalized by FDA July 26, 2011**
1.Risks to Health 2.Device Description 3.Non-Clinical Analysis and Testing 4.Biocompatibility 5.Electrical Equipment Safety 6.Electromagnetic Compatibility 7.Risk Management 8.Clinical Testing 9.Labeling Directions for use Indications for use Contraindications Warnings Precautions Adverse effects Electrical safety Electromagnetic compatibility Caution statement for Prescription use in USA Technical specifications 10.Operational and Process Controls	1.Risks to Health 2.Device Description 3.Non-Clinical Analysis and Testing 4.Biocompatibility 5.Electrical Equipment Safety 6.Electromagnetic Compatibility 7.Software Life Cycle and Risk Management 8.Clinical Testing 9.Labeling Directions for Use Indication for Use Contraindications Warnings Precautions Procedure Precaution Adverse Events Electrical Safety Electromagnetic Compatibility User Training Patient Labeling

Data Assuring Safety and Effectiveness

The FDA is charged with determining "whether the evidence submitted or otherwise available … is valid scientific evidence for purposes of determining the safety and effectiveness of a particular device and whether the evidence, ***when taken as a whole***, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use."

21 CFR 860.7(c)(1). (emphasis added)

EPI's data provided today and in 2009 and 2011 submissions, when taken as a whole, provides more than reasonable assurance that Alpha-Stim® CES is safe and effective.

The Science Supporting CES

Safety

- In 1974, a review of the research on CES was commissioned by the FDA and conducted by the National Research Council, Washington, DC.
- The reviewers concluded “significant side effects or complications attributable” to the application of electric current of approximately one milliampere or less for “therapeutic effect to the head” (*i.e.,* cranial electrotherapy stimulation) were “virtually nonexistent”

  (National Research Council, December 14, 1974, p 42).
- The highest CES current setting on an Alpha-Stim® device is 600 microamperes; 60% of the one milliampere current that the National Research Council reviewers for the FDA considered safe.

Adverse Events Reported to EPI 2007 - 2011

The following tables demonstrate the excellent safety profile of Alpha-Stim® CES over the five year period between 2007 and 2011. **A total of 58,030 Alpha-Stim® devices were sold.** There were 15 reported adverse events during this time frame. Every reported adverse effect was deemed **mild and self-limiting**. Adverse events from using Alpha-Stim® CES reported to EPI in 2007-2011 were **< 1%.** This is consistent with a review of 14 Alpha-Stim® CES studies where adverse events reported from using Alpha-Stim® CES were also **< 1%**. There were no Medical Device Reports (MDR's) reported to FDA during this time.

Adverse Events Summary 2007-2011	N
Skin irritation at electrode site	11
Tinnitus	2
Panic attack	1
Black tongue[1]	1
TOTAL	**15**

Based on the last 5 years sales figure of 58,030 minus returns (there were 75 returns in 2011), an individual home Alpha-Stim user survey[2] and an Alpha-Stim® practitioner survey,[3] using a conservative estimate, during 2007-2011 there was a total of

8,248,920 Alpha-Stim® CES treatments

(1,982,520 individual users treatments plus 6,266,400 in-office treatments by practitioners).

[1] The tongue discoloration was later attributed to medication (Pepto Bismol).

[2] Individual home Alpha-Stim® CES user survey, August 2011, where patients used Alpha-Stim® for an average of 3 months, 3 times per week (36 treatments).

[3] Practitioners in-office treatment survey, December 2011, where practitioners reported an average of 10.1 treatments per week for 48 weeks per year.

Adverse Events Reported in 14 Alpha-Stim® CES Studies (N=2,600) vs. 1 rTMS Study (N=165)

Side effects reported with the use of CES from 14 Alpha-Stim® CES studies encompassing **2,600** subjects, where N = **2,389** (in active CES treatment group, sham/open label group or control/open label group) had treatment while the remaining subjects were in the sham or control groups only:

Adverse Event	CES 2.47%	Sham 1%
Ears tender, tingle, sting, itch, ear clips too tight	**16**	7
Vertigo	**14**	1
Drowsy, sleepy, relaxing	**7**	5
Headache	3	3
Skin Irritation, earlobes	3	0
Nausea	3	0
Agitation/Anger	2	0
Tinnitus	2	0
Metallic taste in mouth	**2**	1
Increased pain	1	1
Legs tingling, burning	1	1
Leg spasms	1	2
Head tingles	0	1
Pins and needles in bladder	1	0
Burning in Buttocks	1	0
Auditory hallucinations	1	0
Heavy feeling	**1**	0
Heart racing, chest pain	0	2
TOTALS	**59**	**24**

All CES adverse events *reported* were 2.47%
However the majority (40; 1.7%) were normal effects.

Adverse Event	Active rTMS (N = 165) N (%)
Headache	96 (58.2)
Application site pain	59 (35.8)
Muscle twitching	34 (20.6)
Anxiety	19 (11.5)
Application site discomfort	18 (10.9)
Nausea	17 (10.3)
TOTALS	**243**

rTMS Study 01: Adverse events with an incidence on Active rTMS of ≥ 10%. *FDA Executive Summary, 2007.*

Comparison of Safety Data of Serious Adverse Events

Alpha-Stim® CES	rTMS Study 01: Serious Adverse Events, Active Treatment, N=165	
None in 31 years on the market	Worsening of major depression	1
	Suicidal ideation	1
	Overdose[1]	5
	Device malfunction/first degree burn	1
	Device malfunction/severe pain at treatment site	1
	All Serious Adverse Events Reported	**9**

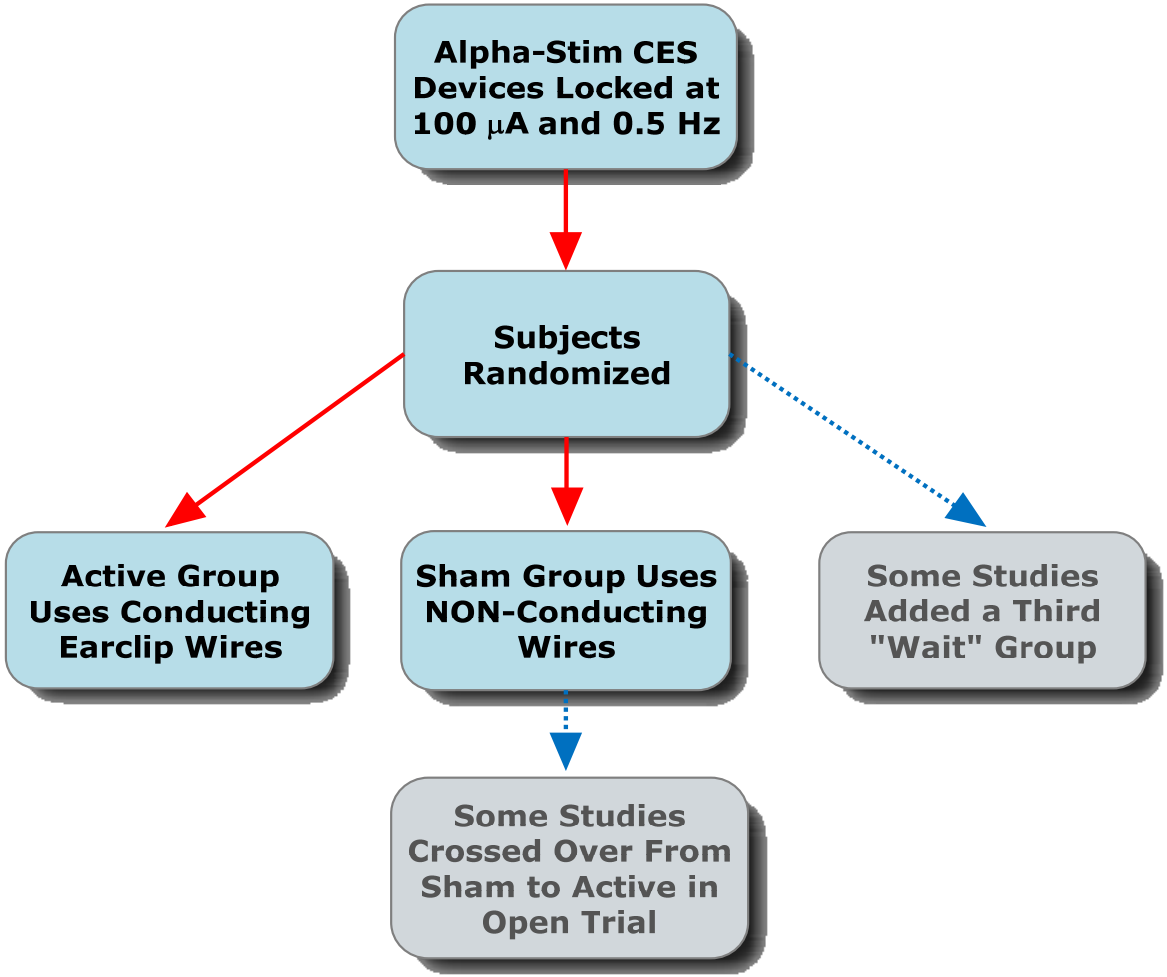
Alpha-Stim® CES is Safe:
All Adverse Events From Every Source Over 3 Decades Have Always Been Minor and Self-limiting and <1%.

[1] Overdose refers to events associated with inadvertent treatment of >75 trains of active TMS delivered to a patient on a single calendar day. The device has been modified so this cannot happen in the rTMS device currently marketed.

Effectiveness of CES

- Findings include only studies that used **Alpha-Stim®** CES devices.
- All studies were **independently conducted** by researchers not associated with EPI.
- EPI loaned CES devices for use in the studies.
  For RCTs, **one-half of the devices did not conduct current**.
  1. The current was set at a **subsensory level** of 100 microamperes for the active CES devices
  2. to compensate the **time was increased to one hour**.
  (*Dosage = current inversely proportional to time*).
  Both subjects and investigators were completely blinded to treatment condition of active or sham.

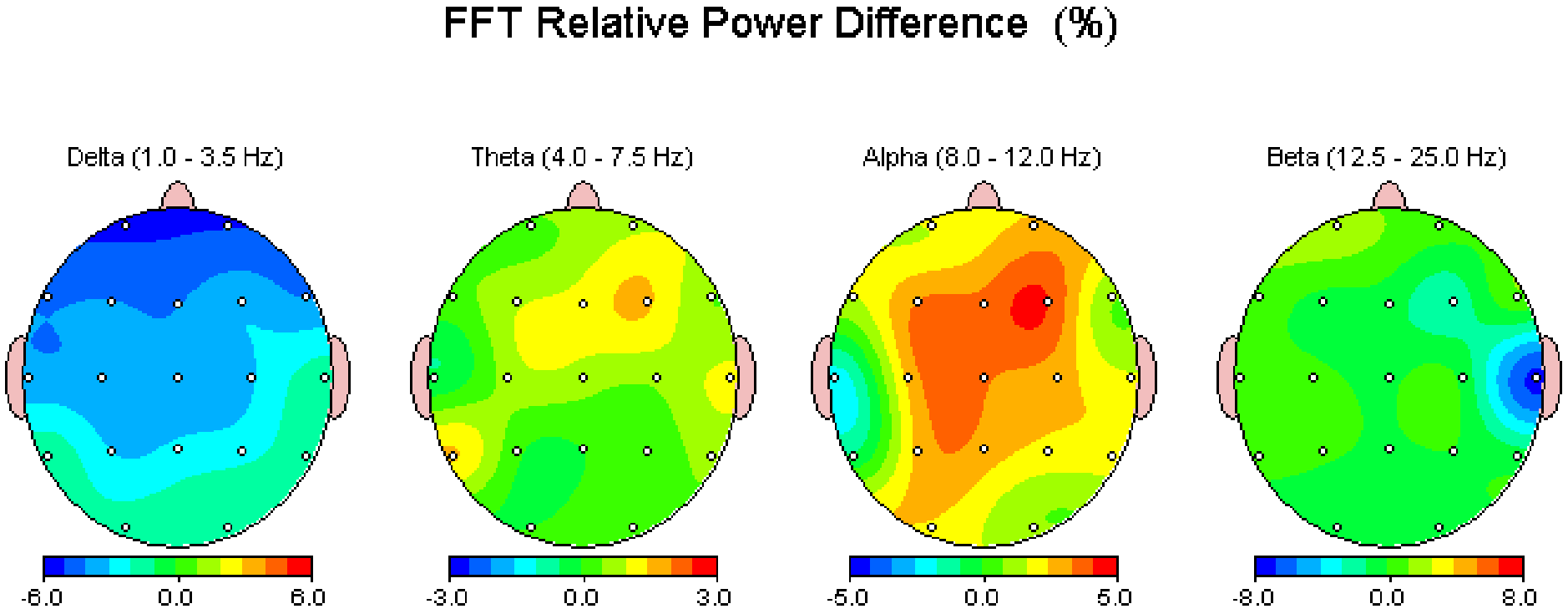
Protocol Used in All Alpha-Stim® CES RCT Double Blind Studies



EEG Changes in 30 Subjects Treated with

A Single 20 Minute Treatment of Alpha-Stim® CES

Blue = decrease There is a decrease in delta activity which means more alert
Red = increase There is an increase in alpha activity which means more relaxed



Kennerly, Richard. QEEG analysis of cranial electrotherapy: a pilot study.
Journal of Neurotherapy, (8)2, 2004.
Presented at the International Society for Neuronal Regulation conference, September 18-21, 2003, Houston, Texas

ALPHA-STIM® CES ANXIETY RCT STUDIES

Anxiety Alpha-Stim® RCT Studies

Principal Investigator	Total N	CES N	Subjects	Study Type	Findings
Kim, H. MD 2008	60	30	Preoperative Patients	RCT, IB	CES group had **significantly** lower scores on Likert anxiety scale than control group at end point of study **(p < 0.01, d = -.88)**
Strentzsch, J. PhD, 2008	38	15	Chronically Mentally Ill Partial Hospitalization Patients	RCT, DB	CES group had **significantly** lower scores on SAI (indicating less state anxiety) than sham group at endpoint of study **(p = 0.02, d = -.41)**. "Wait-in-line" control group had **significantly** lower scores on STI (trait anxiety) than CES group (see PI's explanation below).[1]
Cork, R, MD, PhD, 2004	74	62	Fibromyalgia Patients	RCT, DB, & OL	CES group had **significantly** lower scores on POMS (indicating less anxiety) than sham group at end point of study **(p < 0.01)**. Open label CES group had **significantly** lower scores on POMS at post-test from baseline scores **(p < 0.001)**.
Lichtbroun, A., MD, 2001	60	43	Fibromyalgia Patients	RCT, DB, & OL	CES group had **significantly** lower scores on POMS-A (indicating less anxiety) than sham group at end point of study **(p = 0.02, d = -0.60)**. There was **no significant difference** in Open Label crossover group from pretest to post test on POMS-A **(p > 0.05)**.
Winick, R. DDS, 1999	33	17	Dental Patients	RCT, DB	CES group had **significantly** lower scores (indicating less anxiety) on VAS **(p < 0.02, d = -.61)** and NRS **(p < 0.01)** than sham group at end point of study.
Voris, M. PhD, 1995	105	40	Psychiatric Patients	RCT, DB	CES group had **significantly** lower scores (indicating less anxiety) on SAI than the sham and control groups at end point of study **(p = 0.0001, d = -1.60)**. CES group had **significantly** higher finger temperature scores **(p = 0001, d = 0.50)** and **significantly** lower EMG scores **(p = 0.0001, d = -1.08)**, indicating less anxiety, than sham and control groups.
TOTAL N	**370**	**207**			

IB – Investigator blind, DB – Double blind, OL – Open Label group, Cohen's ***d*** effect sizes: 0.2 = small, 0.5 = medium, 0.8 = large

SAI State Anxiety Inventory, POMS Profile of Mood States, POMS-A Profile of Moods Anxiety Subscale, VAS Visual Analog Scale, NRS Numerical Rating Scale

[1] The Control group reported that they felt "left out" by not wearing ear clips, etc. The investigator said that "People with chronic mental illness struggle daily with feeling 'left out' of society and feeling different, and will frequently report doing well so they will not be perceived as different."

ALPHA-STIM® CES ANXIETY NS STUDY

Anxiety Alpha-Stim® RCT Study, NS Findings					
Principal Investigator	**Total N**	**CES N**	**Subjects**	**Study Type**	**Findings**
Mellen, R. PhD, 2009	21	11	Sheriff's Jail Security and Patrol Officers	RCT, DB	There was **no significant difference** between groups at end point of study on anxiety scores on BAI and BSI-A. ***The researchers inadvertently created a washout period by waiting 1 week after the last CES treatment to take the final anxiety measures. State anxiety is time dependent so waiting one week after the last treatment before taking measurements explains the non-significant finding.*** (The CES group had **significantly** lower depression scores (indicating less depression) on the BDI than sham group, **p < 0.01** at end point of study.)
DB – Double blind					

BAI Beck Anxiety Inventory, BSI-A Brief Symptom Inventory, Anxiety Subscale, BDI Brief Symptom Inventory, Depression Subscale

Alpha-Stim® CES ANXIETY OPEN LABEL

Anxiety Alpha-Stim® Open Label Studies

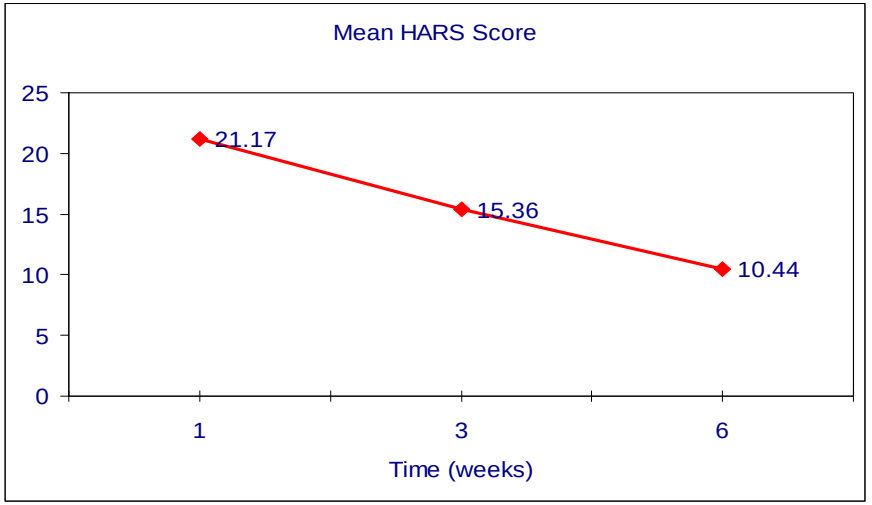
Principal Investigator	Total N	CES N	Subjects	Study Type	Findings
Bystritsky, A., MD, PhD, 2008	12	12	General Anxiety Disorder Patients	OL	Anxiety scores decreased **significantly** on HAM-A from baseline to endpoint of study **(p =.01, d = -1.52)**. Anxiety scores were **significantly** lower on FDADS at end point of study from baseline **(p < 0.01, d = -0.75)**.
Overcash, S., EdD, 1999	197	197	Anxiety Disorder Patients	OL	Subjects rating of anxiety was **significantly** less from baseline to post-test **(p < 0.05)**.Subjects' physiological measures of anxiety – EMG, EDR and Temp – changed **significantly** from baseline to post-test indicating less anxiety **(p < 0.05)**.
N OL	**209**	**209**			
N RCT	**370**	**207**			
TOTAL N	**579**	**416**			

OL- Open Label

HAM-A Hamilton Anxiety Scale,
FDADS Four Dimensional *Anxiety* and Depression Scale

Cohen's ***d*** effect sizes: 0.2 = small, 0.5 = medium, 0.8 = large.

Alpha-Stim CES Significantly Reduced the Symptom Burden of GAD with a Decrease in HARS Score Similar to that Found in Clinical Psychopharmacology Trials Presented at the American Psychiatric Association Meeting 2009



Bystritsky et al, Journal of Clinical Psychiatry, 2008

Alpha-Stim® CES EFFECT SIZES
Anxiety (active versus sham)

MEASUREMENT SCALES

- 0.41 SAI (small) [1]
- 0.60 POMS - A (medium) [2]
- 0.75 FDADS - A (medium) [3]
- 0.61 VAS (medium) [4]
- 0.88 VAS (large) [5]
- 1.52 HAM-A (very large) [3]
- 1.60 SAI (very large) [6]

- 0.91 Pooled Effect Size (large) - 6 Studies

PHYSIOLOGICAL MEASURES

- 1.08 EMG (large) [6]
- 0.50 TEMP (medium) [6]

0.79 Pooled Effect Size

(medium to Large) - 1 Study

[1]Strentzsch, 2008; [2]Lichtbroun, 2001; [3]Bystritsky, 2008; [4]Winick, 1999; [5]Kim, 2008; [6] Voris, 1995.

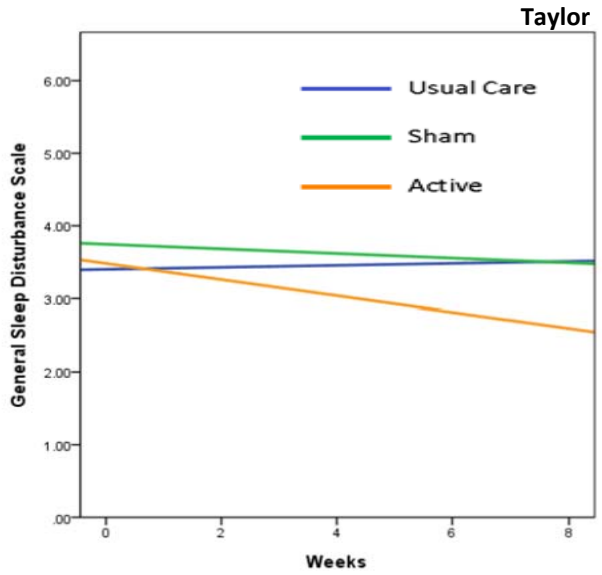
SAI – State Anxiety Inventory; POMS-A – Profile of Mood States-Anxiety Subscale; FDADS – Four Dimensional Anxiety and Depression Scale-Anxiety Subscale; VAS – Visual Analog Scale; HAM-A Hamilton Rating Scale for Anxiety.

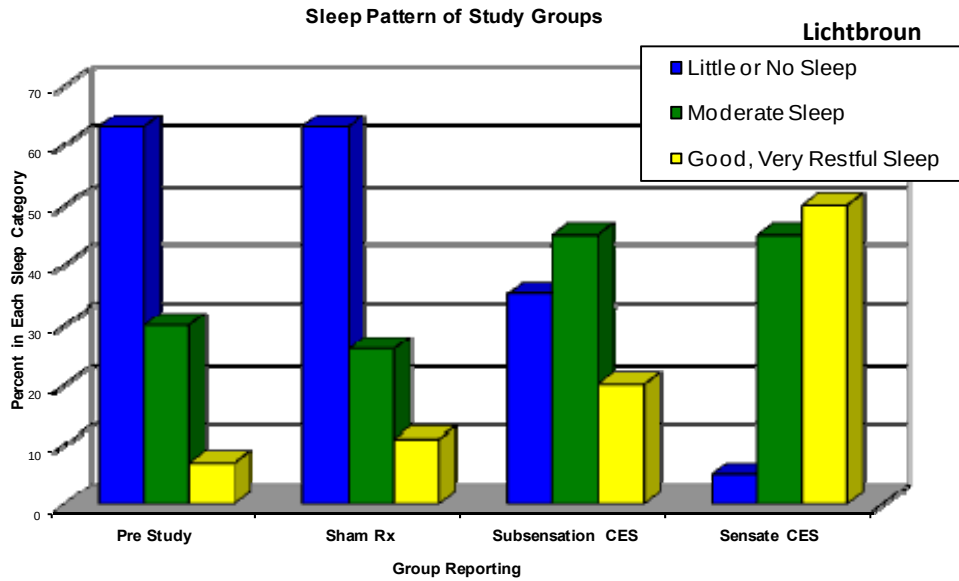
Cohen's ***d*** effect sizes: 0.2 = small, 0.5 = medium, 0.8 = large.

Alpha-Stim® CES INSOMNIA RCT STUDIES

Insomnia Alpha-Stim® RCT Studies					
Principal Investigator	**N**	**CES N**	**Subjects**	**Study Type**	**Findings**
Taylor, A. EdD, 2011	46	17	Fibromyalgia Patients	RCT, DB	CES group had **significantly** lower scores on GRDS (indicating less sleep disturbance) than sham and usual care groups from baseline at end point of study **(p = 0.001, d = -0.30)** and completed the study with scores below the range of insomnia.
Lichtbroun, A., MD, 2001	60	43	Fibromyalgia Patients	RCT, DB & OL	CES group had **significantly** higher scores on the POMS-S than the sham and control groups at end point of study **(p = 0.02, d = 0.54)**.
N RCTs	**106**	**60**			
DB = Double blind, OL = Open Label			Cohen's ***d*** effect sizes: 0.2 = small, 0.5 = medium, 0.8 = large.		

GRDS General Sleep Disturbance Scale, POMS-S Profile of Moods Sleep Subscale





Alpha-Stim® CES DEPRESSION STUDIES

Depression Alpha-Stim® RCT Study					
Principal Investigator	**N**	**CES N**	**Subjects**	**Study Type**	**Findings**
Mellen, R., PhD, 2009	21	11	Sheriff's Jail Security and Patrol Officers	RCT, DB	CES group had **significantly** less depression than sham group at end point of study on BDI **($p < 0.01$)** and on BSI-D **($p < .05$).**
N RCT	**21**	**11**			

Depression Alpha-Stim® Open Label Study					
Principal Investigator	**N**	**CES N**	**Subjects**	**Study Type**	**Findings**
Bystritsky, A., MD, PhD, 2008	12	12	Generalized Anxiety Disorder Patients	OL	Depression scores were **significantly** less on $HAM\text{-}D_{17}$ at end point of study from baseline **($p < 0.01$)**.
N OL	**12**	**12**			

DB – Double blind, OL – Open Label group

BDI Beck Depression Inventory
BSI-D Brief Symptom Inventory – Depression
$HAM\text{-}D_{17}$ Hamilton Depression $Scale_{17}$

Ongoing Federally Funded RCT, Double-Blind, Placebo Controlled Alpha-Stim® CES Studies on Anxiety, Insomnia, Depression

Institution	Patients	Outcome Variables
Brook Army Medical Center, San Antonio *Funded by the DOD*	PTSD Patients	Anxiety, Insomnia, Depression, Irritability, Pain
Darnall Army Medical Center, Fort Hood *Funded by the DOD*	PTSD Active Duty Service Members	Anxiety, Insomnia, Depression, PTSD symptomology, Medication
Walter Reed Army Medical Center, Bethesda *Funded by the DOD*	Active Duty Service Members	Insomnia
Landstuhl Army Regional Medical Center, Germany *Funded by the DOD*	Active Duty Service Members	Insomnia
Michael E. DeBakey VA Medical Center and Baylor University *Funded by the VA Medical Centers*	Mild Traumatic Brain Injury Patients	Anxiety, Insomnia, Depression, Pain
Virginia Commonwealth University School of Nursing *Funded by the National Cancer Institute*.	Breast Cancer Patients	Anxiety, Insomnia, Depression

A Single Question With Either a Likert Scale or VAS Adequately Measured State Anxiety

Objective

To determine whether a single question with a Likert Scale or a Visual Analog Scale (VAS) response adequately measures current anxiety.

Study Design and Setting

Consecutive English-speaking adult women attending a dedicated breast clinic in a major Australian city were invited to complete a demographic questionnaire, the State Trait Anxiety Inventory (STAI), and a single question with a five-point Likert Scale response and a VAS in random order. Only women who completed the STAI were included in analyses.

Results

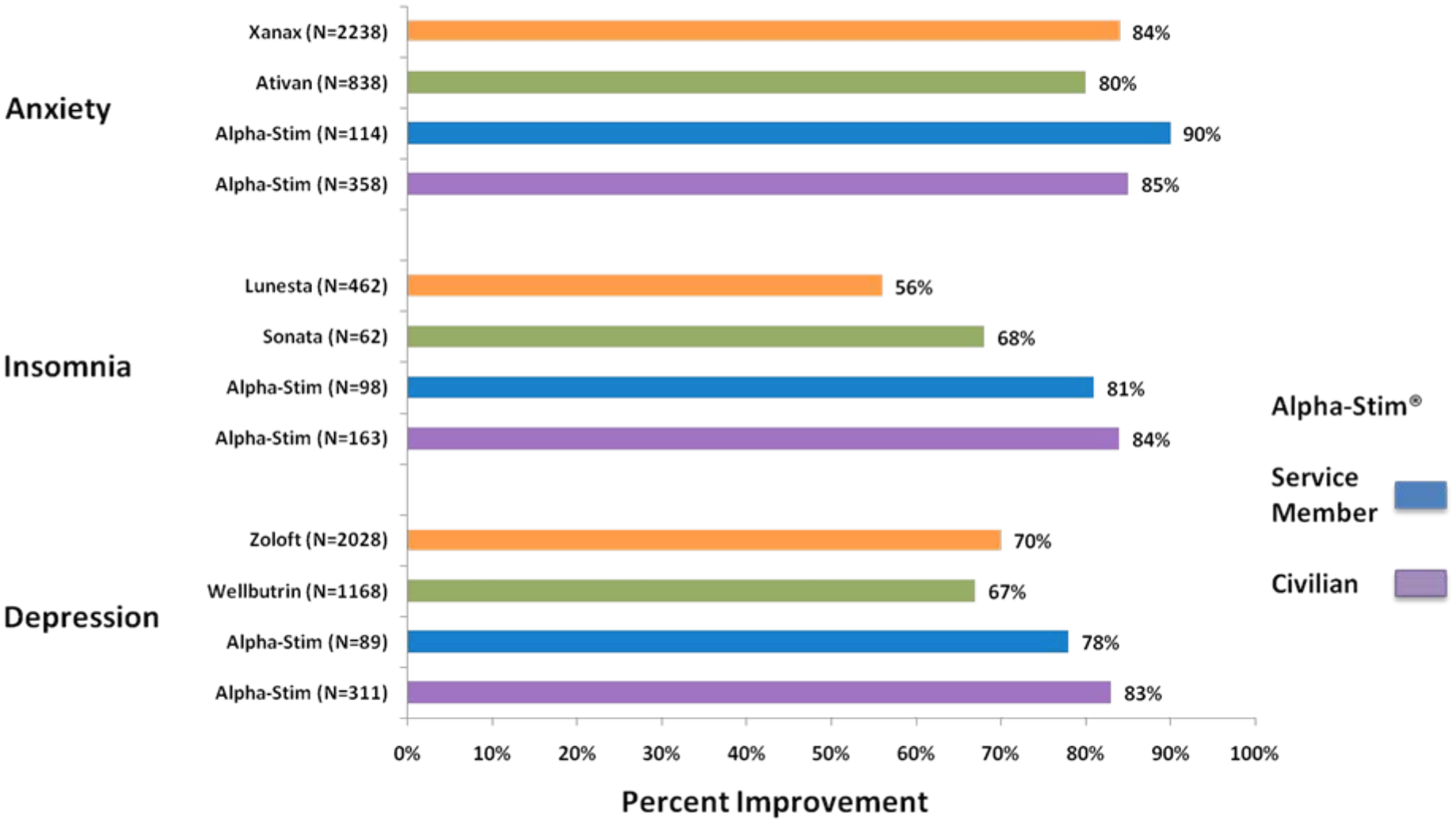
Four hundred of 497 (80%) eligible women agreed to participate. Both measures were adequate predictors of the STAI score; ***correlation with STAI was 0.78 (95% confidence interval [CI] 0.73–0.82) for the VAS and 0.75 (95% CI 0.70–0.79) for the Likert Scale***. However, 11% of women incorrectly completed the VAS limiting its usefulness.

Conclusion

A single question with either a Likert Scale or VAS response may be an adequate replacement for the STAI. ***Both measures quickly and easily assess anxiety and may be useful for research purposes*** when researchers have very limited time or questionnaire space or need to reduce the burden on participants of completing many measures.

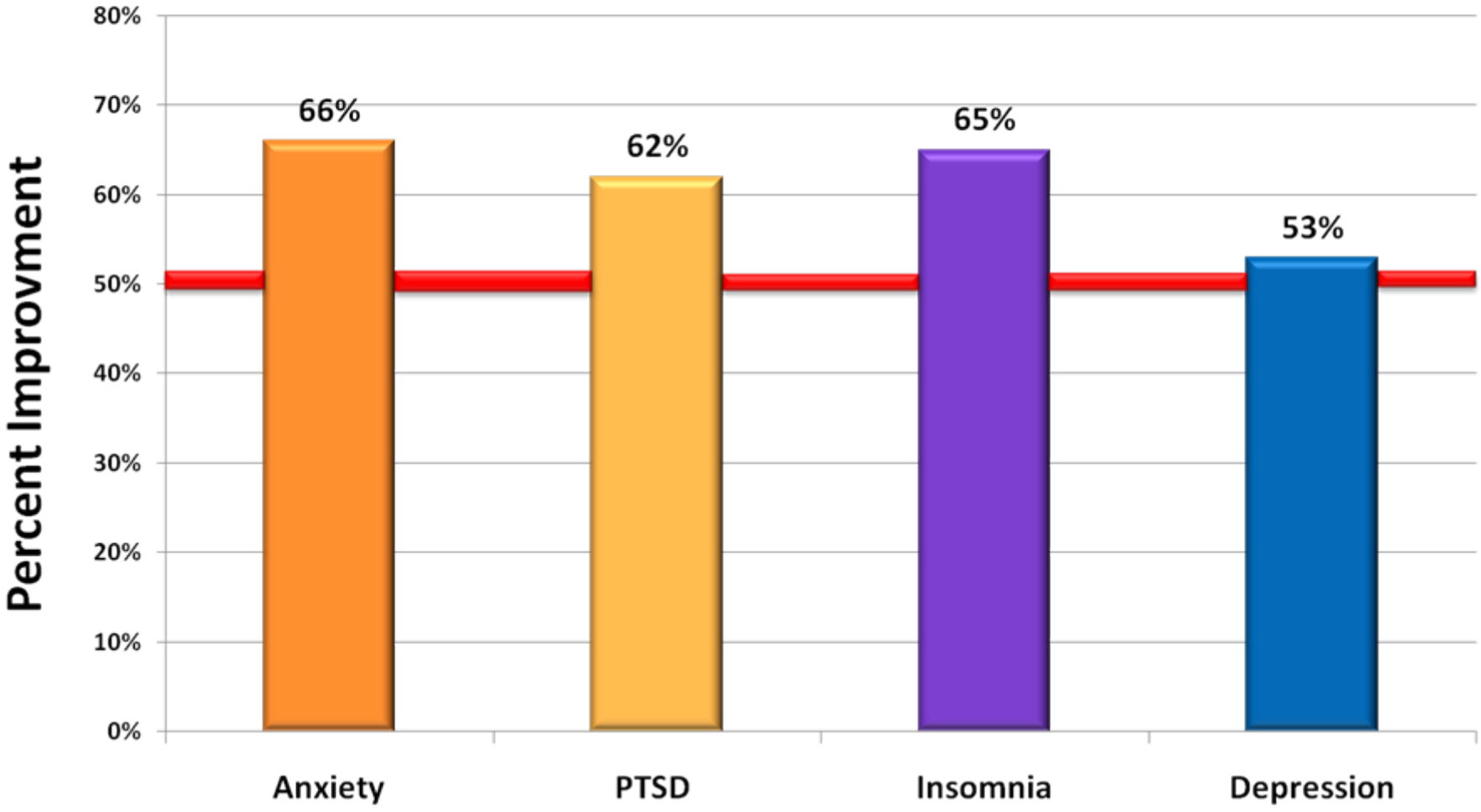
Davey, Heather M., Barratt, Alexandra L., Butow, Phyllis N., Deeks, Jonathan J. A one-item question with a Likert or Visual Analog Scale adequately measured current anxiety. *Journal of Clinical Epidemiology*. 60(4):356-360, 2007.

2011 Military Service Member and Civilian Postmarketing Surveys: Alpha-Stim® CES Compared to WebMD Drug Surveys



Alpha-Stim Data from October 2011 Military Service Member Survey Analysis (N=152) and Alpha-Stim Patient Survey (N=1,745) October 2011
Conducted by Larry Price PhD, Associate Dean of Research and Professor of Psychometrics and Statistics, Texas State University.
Pharmaceutical Survey Data from: www.WebMD.com/drugs. Accessed on October 28th, 2011.

Clinical Improvement of Substantial Importance from Service Members' Self Reports

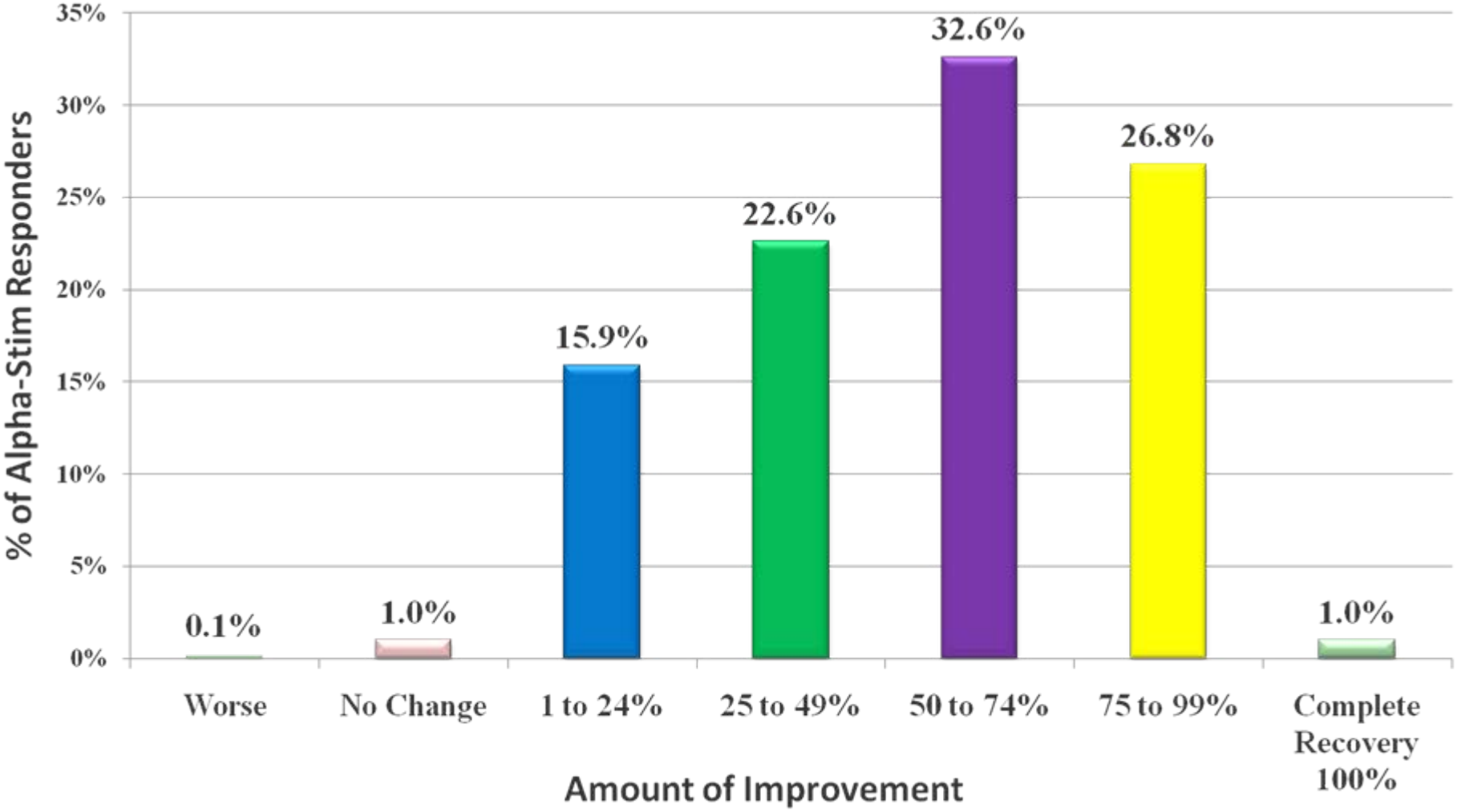


30-49% is considered moderate clinical importance
≥ 50% is considered substantial clinical importance

Dworkin, R.H., Turk. D.C., Wyrwich, K.W., Beaton, D., Cleeland, C.S., & Farrar, J.T., et. al. (2008). Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials. IMMPAC recommendations. *Journal of Pain*, 9 (2), 103-121.

2011 Alpha-Stim Patient Survey, N=1,745

60% Improved At Least 50%



Comparison of Effectiveness Data

CES Effectiveness: Anxiety

- 6 RCTs: 5 double-blind sham controlled RCT studies, 1 RCT investigator-blind study, Total **N = 370**.
- CES group had **significantly** lower scores at end point of study on primary measures of anxiety than sham group in all 6 studies, p for all studies ranged from **p = 0.0001 to p = 0.02**.
- 2 OL Studies, Total N = 209 CES group had **significantly** lower scores on primary anxiety measure at primary end point of study in both studies from baseline, **p = 0.01** and **p < 0.05**.

rTMS Effectiveness: Depression

- 1 "triple-blind", sham-controlled RCT Study, **N = 301**.
- **No significant difference** on primary outcome measure of depression (MADRS) between rTMS and sham groups at end point of study, **p = 0.057**. FDA described this as "**minimally clinically interesting difference between the treatment groups.**"
- Post-hoc analysis excluding scores ≤ 20 on MADRS for 6 subjects (4 in rTMS group and 2 in sham group) at end point of study was done, the adjusted MADRS score was **significant**, **p = 0.038 on reanalysis**.
- rTMS group had **significantly** lower depression scores than sham group on secondary specific depression outcome, HAM-D_{24}, **p = 0.012** and HAM-D_{17}, **p = 0.006** at end point of study. IDS-SR depression scores approached significance, **p = 0.058,** at end point of study.
- **rTMS was classified to Class II, July 2011.**

Data from FDA Executive Summary, rTMS 2007

Comparison of Effect Sizes

CES: Anxiety

(from previous slide)

- 0.41 SAI (small)
- 0.60 POMS - A (medium)
- 0.75 FDADS - A (medium)
- 0.61 VAS (medium)
- 0.88 VAS (large)
- 1.52 HAM-A (very large)
- 1.60 SAI (very large)

- 0.91 Pooled Effect Size (large) - 6 Studies

rTMS: Depression

-0.355 MADRS (small)

-0.481 $HAMD_{24}$ (small)

-0.556 $HAMD_{17}$ (medium)

MADRS, Montgomery-Asperg Depression Rating Scale
HAMD, Hamilton Depression Rating Scale

Cohen's ***d*** effect sizes: 0.2 = small, 0.5 = medium, 0.8 = large

Based on Alpha-Stim® Research Studies, When Taken as a Whole, 10 CES Studies Provide Significant Results Supporting a Finding of Reasonable Assurance of Safety and Effectiveness

- **Alpha-Stim® CES is Safe and Effective** for the treatment of anxiety, insomnia and depression.
- Alpha-Stim® CES adverse events were mild, self-limiting and < **1%** compared to rTMS adverse events that were ≥ **10%.**
- Alpha-Stim® CES: **No** serious adverse events in 31 years on the market. rTMS: **9** serious adverse events were reported in Study 01, N=301.
- There are 10 Alpha-Stim® studies with significant results supporting the effectiveness of CES: 8 RCTS (N = 437) and 2 Open Label Studies (N = 209). There was 1 RCT study (N = 301) supporting the effectiveness of rTMS. (FDA Executive Summary, rTMS 2007).
- TMS was down-classified to Class II, July 2011.

We have seen that there is reasonable assurance of safety and effectiveness for Alpha-Stim® CES and no evidence or experience to the contrary in 31 years.

Therefore we respectfully request that you recommend down classification to Class II for Alpha-Stim® CES Technology for anxiety, insomnia and depression.